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L6: Entry 83 of 94 File: USPT Apr 18, 1995

DOCUMENT-IDENTIFIER: US 5407609 A
TITLE: Microencapsulation process and products therefrom

Brief Summary Text (11):
Another emulsion-based method to prepare microspheres described in U.S. Pat. No. 3,737,337 uses a controlled extraction of the polymer solvent from the microdroplets by adding processing medium to the emulsion at a controlled rate. However, this patent teaches away from the present invention by disclosing that the extraction must proceed slowly or no spherical particles will be formed. Similarly, U.S. Pat. No. 4,652,441 describes a method to encapsulate water-soluble agents from water-in-oil-in-water emulsions, and teaches that a high-viscosity, drug-retaining substance must be included in the inner water phase to retain the drug in the microdroplets during evaporation of the polymer solvent. U.S. Pat. No. 4,652,441 also teaches against the present invention by suggesting that it is impossible to effectively encapsulate water-soluble agents without using drug-retaining substances in the emulsion.

Brief Summary Text (13):
Accordingly, one object of the present invention is to provide an emulsion-based method for preparing microspheres with agents that have a high propensity to partition within minutes into the processing medium, the continuous phase of the emulsion. Yet another object of the present invention is a method to prepare microcapsules, as well as microspheres, from an emulsion. Yet another object of the invention is to provide a method for preparing microspheres or microcapsules containing an agent that has a solubility of greater than 10 milligrams per milliliter in the processing medium. Yet another object of the invention is to control the porosity of the wall of microcapsules or excipient of microspheres by controlling the rate of extraction of the solvent from the microdroplets of the emulsion. Yet another object of the present invention is to provide a method for making microcapsules and microspheres having diameters from less than 1 micron to greater than 2 millimeters. Still another object of the present invention is to provide a method for preparing drug-loaded microspheres and microcapsules that result in free-flowing powders of unagglomerated spherical particles suitable for parenteral as well as other routes of drug administration.

Detailed Description Text (6):
The liquid, or solid agent to be encapsulated is then dispersed or dissolved in the solvent containing the dissolved wall-forming material or excipient. Examples of biological agents that may be encapsulated by this technique include, but are not limited to, analgesics such as acetaminophen, acetylsalicylic acid, and the like; anesthetics such as lidocaine, xylocaine, and the like; anorexics such as dexedrine, phendimetrazine tartrate, and the like; antiarthritics such as methylprednisolone, ibuprofen, and the like; antiasthmatics such as terbutaline sulfate, theophylline, ephedrine, and the like; antibiotics such as sulfisoxazole, penicillin G, ampicillin, cephalosporins, amikacin, gentamicin, tetracyclines, chloramphenicol, erytromycin, clindamycin, isoniazid, rifampin, and the like; antifungals such as amphotericin B, nystatin, ketoconazole, and the like; antivirals such as acyclovir, amantadine, and the like; anticancer agents such as cyclophosphamide, methotrexate, etretinate, and the like; anticoagulants such as heparin, warfarin, and the like; anticonvulsants such as phenytoin sodium, diazepam, and the like; antidepressants such as isocarboxazid, amoxapine, and the like; antihistamines such as diphenhydramine HCl, chlorpheniramine maleate, and the like; hormones such as

insulin, progestins, estrogens, corticoids, glucocorticoids, androgens, and the like; tranquilizers such as thorazine, diazepam, chlorpromazine HCl, reserpine, chlordiazepoxide HCl, and the like; antispasmodics such as belladonna alkaloids, dicyclomine hydrochloride, and the like; vitamins and minerals such as essential amino acids, calcium, iron, potassium, zinc, vitamin B.sub.12, and the like; cardiovascular agents such as prazosin HCl, nitroglycerin, propranolol HCl, hydralazine HCl, verapamil HCl, and the like; enzymes such as lactase, pancrelipase, succinic acid dehydrogenase, and the like; peptides and proteins such as LHRH, somatostatin, calcitonin, growth hormone, growth releasing factor, angiotensin, FSH, EGF, vasopressin, ACTH, human serum albumin, gamma globulin, and the like; prostaglandins; nucleic acids; carbohydrates; fats; narcotics such as morphine, codeine, and the like; psychotherapeutics; anti-malarials; L-dopa, diuretics such as furosemide, spironolactone, and the like; antiulcer drugs such as ranitidine HCl, cimetidine HCl, and the like.

Detailed Description Text (15):
Because water-soluble agents, such as peptides and proteins, do not diffuse through hydrophobic wall-forming materials such as the lactide/glycolide copolymers, pores must be created in the microcapsule or microsphere membrane to allow these agents to diffuse out for controlled-release applications. Several factors will affect the porosity obtained. The amount of agent that is encapsulated affects the porosity of microspheres. Obviously, higher-loaded microspheres (i.e., greater than about 20 wt. %, and preferably between 20 wt. % and 80 wt. %) will be more porous than microspheres containing smaller amounts of agent (i.e., less than about 20 wt. %) because more regions of drug are present throughout the microspheres. The ratio of agent to wall-forming material that can be incorporated into the microspheres can be as low as 0.1% to as high as 80%. Obviously, the loading that can be obtained for specific agents will depend to some extent on the physical properties of the agent and the desired application for the microsphere formulation.

Detailed Description Text (30):
Approximately 2.5 g of poly(DL-lactide)(DL-PL) was dissolved in the appropriate quantity of methylene chloride to prepare an 11.1 wt. % polymer solution. After the polymer was completely dissolved, a predetermined quantity of testosterone propionate was added and allowed to dissolve. This polymer/drug solution was then poured into a 1-L resin kettle containing 400 g of 5.0 wt. % PVA. The PVA was being stirred at about 750 rpm by a 2.5 in. TEFLON impeller driven by a Fisher Stedi-speed motor. The PVA was also saturated with 7 mL of methylene chloride prior to the addition of the polymer/drug solution. The resulting emulsion was allowed to stir for 7 min., after which the resin kettle contents were transferred all at once to 12.0 L of stirring deionized water. The microspheres were stirred in the deionized water for approximately 30 min and then were collected over 45-.mu.m and 212-.mu.m stainless steel mesh steel sieves arranged in series. The microspheres were rinsed with additional deionized water and allowed to air dry.

Other Reference Publication (2):
E. Mathiowitz et al., "Polyanhydride Microspheres as Drug Carriers", J. of Appl. Polymer Sci., 35:755-774 (1988).

Other Reference Publication (3):
Toyomi Sato et al., "Porous Bidoegradable Microspheres for Controlled Drug Delivery", Pharm. Research, 5:21-30 (1988).

CLAIMS:

51. The method of claim 1, wherein the microencapsulated agent is an analgesic, anesthetic, anorexic, antiarthritic, antiasthmatic, antibiotic, antifungal, antiviral, anticancer agent, anticoagulant, anticonvulsant, antidepressant, antihistamine, hormone, tranquilizer, antispasmodic, vitamin, mineral, cardiovascular agent, enzyme, peptide, protein, prostaglandin, nucleic acid, carbohydrate, fat, narcotic, psychotherapeutic, antimalarial, L-dopa, diuretic, antiulcer drug, or immunological agent.

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L6: Entry 74 of 94 File: USPT Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6036976 A
TITLE: Sustained release microspheres and preparation thereof

Brief Summary Text (3):
As a prior art technology, a sustained-release preparation comprising a drug, a polylactic acid and a glycolic acid/hydroxycarboxylic acid [HOCH(C.sub.2 -C.sub.8 alkyl)COOH] copolymer is described in EP-A-481,732, for instance. As a production method for said preparation, the in-water drying method is described in which a w/o emulsion, comprising an aqueous solution of a physiologically active peptide as an internal aqueous phase and an organic solvent solution of a biodegradable polymer as an oil phase, is added to water or the like to yield a w/o/w emulsion, from which sustained-release microspheres are produced.

Brief Summary Text (5):
In in-water drying, insufficient solvent removal, due to the unsatisfactory speed of solvent removal from microspheres, is likely to cause sphere aggregation, resulting in problems regarding the dispersibility of spheres and the needle passability during administration. An attempt to achieve sufficient solvent removal results in significantly extended in-water drying time, which in turn decreases the drug entrapment ratio in the microspheres obtained and cannot bring satisfactory results.

Brief Summary Text (7):
Through intensive investigation against this background, the present inventors found it possible to increase the speed of solvent removal from microspheres and markedly improve the drug entrapment ratio in microspheres by subjecting the microcapsules to in-water drying under particular condition, and developed the present invention.

Brief Summary Text (20):
Microspheres of the present invention are not limited as long as they are fine particles (microspheres) comprising a physiologically active substance (hereafter also referred to as drug) and a biodegradable polymer.

Brief Summary Text (22):
Physiologically active substances include, but are not limited to, physiologically active peptides, antitumor agents, antibiotics, antipyretic agents, analgesics, anti-inflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptics, antiulcer agents, antidepressants, anti-allergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetics, antihyperlipidemic agents, anticoagulants, hemolytics, antituberculosis agents, hormones, narcotic antagonists, bone resorption suppressors, osteogenesis promoters and angiogenesis inhibitors.

Brief Summary Text (49):
Examples of the antiulcer agents include metoclopramide and histidine hydrochloride.

Brief Summary Text (99):
To facilitate entrapment of a physiologically active substance in microspheres, a drug-retaining substance such as gelatin, agar, sodium alginate, polyvinyl alcohol, a basic amino acid (e.g., arginine, histidine, lysine) and the like may be added in an internal aqueous phase, if necessary. The amount of a drug-retaining substance

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L4: Entry 411 of 422 File: USPT Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972389 A
TITLE: Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter

Brief Summary Text (9):
In another embodiment, the present invention provides a controlled-release oral drug dosage form for releasing a vesicle-containing vesicle, i.e., insoluble, particulate matter, into the stomach, the dosage form comprising a plurality of solid particles of the vesicle-containing drug dispersed within a polymer that (i) swells unrestrained dimensionally via imbibition of water from gastric fluid to increase the size of the particles to promote gastric retention in the stomach of a patient in which the fed mode has been induced, (ii) gradually erodes over a time period of hours, the erosion commencing upon contact with the gastric fluid, and (iii) releases the insoluble particulate matter to the stomach and duodenum at a rate dependent on the erosion rate. Insoluble, particulate matter suitable for use in this embodiment include, but is not limited to, liposomes, nanoparticles, nanospheres and nanocapsules. For example, liposomes encapsulating an acid-labile or enzyme-labile soluble drug, such as a proteinaceous hormone (e.g., calcitonin), an antigen, a peptide, or other drugs that otherwise would require administration by injection, such as erythropoietin, can be dispersed within a polymer to form an erodible, gastric-retentive drug dosage form of the present invention. In this regard, the erodible, gastric-retentive drug dosage form has the added beneficial properties associated with the use of vesicles. Such beneficial properties include protecting drugs against the degradative environment of the G.I. tract, overcoming a too rapid drug release rate due to high drug solubility, or targeting drugs to specific areas within the G.I. tract, such as Peyer's patches.

Detailed Description Text (3):
To overcome these problems, the erodible, gastric-retentive dosage forms of the present invention have been developed. The dosage forms of the present invention are effective for the continuous, controlled administration of drugs which have a low or sparing solubility in gastric fluid, and which are capable of acting either locally within the gastrointestinal tract, or systemically by absorption into circulation via the gastrointestinal mucosa. In addition, the dosage forms of the present invention are useful for delivering drugs incorporated into vesicles, such as liposomes, nanoparticles, proteinoid microspheres, pharmacosomes, etc. The dosage forms of the present invention are also useful for delivering drugs that have been granulated or coated with enteric coating material, so that they pass from the acid environment of the stomach before they can dissolve and become available for absorption. In this manner, the drugs are protected from acid and enzymes during the stomach transit time, so that they arrive intact in the upper part of the small intestine, yet in a controlled manner, due to the dosage form. As such, the dosage forms of the present invention generally consist of a drug or, alternatively, either a drug incorporated into a protective vesicle, or protected by an enteric coating, in combination with an erodible polymer that swells upon contact with the gastric fluid of the stomach.

Detailed Description Text (7):
The term "drug" is used herein to refer to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor

from eliciting a physiological response. The term "antigen," as used herein, refers to a drug that elicits an immune response. Moreover, the term "sparingly soluble," as used herein, refers to a drug having a solubility (measured in water at 37.degree. C.) in the range of 0.001% to about 2% by weight, more preferably 0.001% to 0.5% by weight. The term "soluble", as used herein, refers to a drug having a solubility (measured in water at 37.degree. C.) in the range of 2% to about 10% by weight, more preferably 2% to 5% by weight. The term "vesicle," as used herein, refers to a small (usually 0.01 to 1.0 mm), usually spherical, membrane-bound structure which may contain or be composed of either lipoidal or aqueous material, or both. Suitable vesicles include, but are not limited to, liposomes, nanoparticles, nanospheres, nanocapsules and microspheres composed of amino acids.

Detailed Description Text (13):
As previously mentioned, the dosage forms of the present invention are particularly useful for delivering sparingly soluble drugs. However, in another embodiment, the dosage forms of the present invention can be used to deliver a drug incorporated into a protective vesicle. In this embodiment, the drug can be a sparingly soluble drug or, alternatively, a soluble drug which is rendered sparingly soluble or insoluble when incorporated into the protective vesicles. Suitable vesicles include, but are not limited to, liposomes, nanoparticles, nanospheres, nanocapsules and microspheres composed of amino acids.

Detailed Description Text (16):
Further examples of such vesicles include microparticulate systems which are exemplified by nanoparticles and proteinoid and amino acid microspheres and pharmacosomes. Nanoparticles include, for example, nanospheres and nanocapsules. The matrix-like structure of the nanosphere allows the drug to be contained either within the matrix or coated on the outside. Nanocapsules have a shell of polymeric material and, as with the nanospheres, the drug can be contained either within the shell or coated on the outside. Polymers which can be used to prepare the nanoparticles include, but are not limited to, polyacrylamide, poly(alkyl methacrylates), poly(alkyl cyanoacrylates), polyglutaraldehyde, poly(lactide-co-glycolide) and albumin. For details pertaining to nanoparticle preparation, see, e.g., Allemann, E., et al., Drug-Loaded Nanoparticles--Preparation Methods and Drug Targeting Issues, Eur. J. Pharm. Biopharm., 39(5):173-191, 193, incorporated herein by reference.

Detailed Description Text (58):
200 mg of a mixture of egg lecithin, cholesterol, and phosphatidyl glycerol in the molar ratio of 0.9:1.0:0.1 are added to 100 ml of an organic solvent consisting of 2:1 chloroform:methanol. This lipid solution is evaporated to dryness in a rotary evaporator with a vacuum for a period of time sufficient to assure loss of all chloroform. The residue is then dissolved in 100 ml of ether. 200 mg of zidovudine is dissolved in 50 ml of distilled water, and the solution heated to 55.degree. C. The ether solution is injected below the surface of the warm aqueous solution at an approximate rate of 0.1 ml per minute using a 22 g. hypodermic needle. The liposomes formed are collected by centrifugation, washed with distilled water and dried under vacuum. The concentration of zidovudine in the liposomes is determined by assay following destruction of a weighed sample by action of an organic solvent.

CLAIMS:

16. The dosage form in accordance with claim 15 wherein said vesicle is a member selected from the group consisting of liposomes, nanoparticles, pharmacosomes and proteinoid or amino acid microspheres.

added is normally 0.01 to 10 times by weight that of the physiologically active substance.

Brief Summary Text (111):
The relation between an external aqueous phase and micropheres is represented by, for example, the relation of the volume of the external aqueous phase and the amount of micropheres (total weight amount of a physiologically active substance, a drug-retaining substance and a biodegradable polymer), and the amount of microspheres per m.sup.3 of an external aqueous phase is normally about 0.1 to about 500 kg, preferably about 0.5 to about 100 kg, and more preferably about 1.0 to about 20 kg.

Detailed Description Text (12):
After in-water drying, microspheres were then collected via centrifugation and freeze dried. By nitrogen blowing, the drug entrapment ratio in microspheres was increased by 4%, in comparison with microspheres prepared without nitrogen blowing.

CLAIMS:

11. The microsphere according to claim 1, wherein the physiologically active substance is a substance selected from the group consisting of LH-RH agonist, LH-RH antagonist, antitumor agent, antibiotic, antipyretic agent, analgesic, anti-inflammatory agent, antitussive expectorant, sedative, muscle relaxant, antiepileptic, antiulcer agent, antidepressant, anti-allergic agent, cardiotonic, antiarrhythmic agent, vasodilator, hypotensive diuretic, antidiabetic, antihyperlipidemic agent, anticoagulant, hemolytic, antituberculosis agent, hormone, narcotic antagonist, bone resorption suppressor, osteogenesis promoter and angiogenesis inhibitor.

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L6: Entry 68 of 94 File: USPT Dec 12, 2000

DOCUMENT-IDENTIFIER: US 6159502 A
TITLE: Oral delivery systems for microparticles

Brief Summary Text (23):
Furthermore, in order for either carrier system to work effectively the conjugated material (hormone, peptide or drug) must preferably be able to survive the proteolytic environment of the small intestine and must also contain a suitable site for chemical cross-linkage to the carrier. During the conjugation, care must be taken to preserve the pharmacological activity of the active agent both during the conjugation as well as in the final complex. Furthermore, a number of peptides may not be suitable for oral delivery (due to sensitivity to proteolysis, or due to lack of suitable functional groups for conjugation) and so new analogues may need to be developed which possess an appropriate conjugation site or have been designed to resist proteolytic degradation. In this respect the present invention can be distinguished from the previous inventions described above in that the carrier molecule of the present invention is not covalently conjugated to the pharmaceutically active agent, but rather the carrier molecule is either covalently linked to the material/polymer comprising the microsphere, or is associated hydrophobically with the surface of the microsphere during its formation.

Brief Summary Text (37):
A particularly desired form of the complex of the first embodiment of the present invention is a microsphere or microcapsule coupled to a carrier molecule, the microsphere or microcapsule enclosing a hormone, drug, immunogen, or DNA or RNA (such as ribozyme) component, molecule or analogues thereof, wherein the carrier molecule is a mucosal binding protein or Vitamin B.sub.12, or an analogue or derivative of Vitamin B.sub.12 possessing binding activity to Castle's intrinsic factor.

Brief Summary Text (54):
A preferable composition of the fifth embodiment is a medicament comprising a carrier coupled to a microsphere or microcapsule comprising a hormone, drug, immunogen or DNA or RNA (such as ribozyme) component, molecule or analogues thereof in pharmaceutically active form.

Brief Summary Text (61):
A preferred method of the seventh embodiment is for treating a vertebrate host by administration of a hormone, drug, immunogen or DNA or RNA (such as ribozyme) component, molecule, analogue or derivative thereof requiring such administration which method comprises the oral administration to the host of an effective amount of a carrier coupled to a microsphere or microcapsule comprising a hormone, drug, immunogen or DNA or RNA (such as ribozyme) component, molecule, analogue or derivative thereof appropriate to the therapy of the host.

Brief Summary Text (70):
Hormones, drugs, immunogens or DNA or RNA (such as ribozyme) component, molecule or analogues thereof suitable to be incorporated within a microparticle, such as a microsphere or microcapsule include all hormones, drugs, immunogens or DNA or RNA (such as ribozyme) component, molecule or analogues thereof for which oral administration is desirable but for which oral administration in an unprotected form results in substantial loss of efficacy.

Brief Summary Text (75):
The aforementioned antipyretic, analgesic and antiinflammatory drugs include, for instance, sodium salicylate, sulpyrine, sodium flufenamate, sodium diclofenac, sodium indomethacin, morphine hydrochloride, pethidine hydrochloride, levorphanol tartrate and oxymorphone. Examples of the antitussives and expectorants may be mentioned ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, alloclamide hydrochloride, chlophedianol hydrochloride, picoperidamine hydrochloride, cloperastine, protokylol hydrochloride, isoproterenol hydrochloride, salbutamol sulfate and terbutaline sulfate. Examples of sedatives include chlorpromazine hydrochloride, prochlorperazine, trifluoperazine, atropine sulfate and scopolamine methylbromide. The muscle relaxants include, among others, pridinol methanesulfonate, tubocurarine chloride and pancuronium bromide. The antiepileptics include, for instance, sodium phenytoin, ethosuximide, sodium acetazolamide and chlordiazepoxide hydrochloride. Examples of antiulcer drugs include metoclopramide and L-histidine monohydrochloride. Examples of antidepressants include imipramine, clomipramine, noxiptiline and phenelzine sulfate. The antiallergic drugs include, among others, diphenhydramine hydrochloride, chlorpheniramine maleate, tripelenamine hydrochloride, methdilazine hydrochloride, clemizole hydrochloride, diphenylpyraline hydrochloride and methoxyphenamine hydrochloride. The cardiotonics include, among others, trans-p-oxocamphor, theophyllol, aminophylline and etilefrine hydrochloride. The antiarrythmic agents include, for instance, propranolol hydrochloride, alprenolol hydrochloride, bufetolol hydrochloride and oxyprenolol hydrochloride. The vasodilators include, among others, oxyfedrine hydrochloride, diltiazem hydrochloride, tolazoline hydrochloride, hexobendine and bamethan sulfate. The antihypertensive diuretics include, among others, hexamethonium bromide, pentolinium, mecamlamine hydrochloride, ecarazine hydrochloride and clonidine hydrochloride. Examples of antidiabetics include sodium glymidine, glypizide, phenformin hydrochloride, buformin hydrochloride and metformin. The anticoagulants include, among others, sodium heparin and sodium citrate. The haemostatic agents include, among others, thromboplastin, thrombin, menadione sodium bisulfite, acetomenaphthone, e-amino-caproic acid, tranexamic acid, carbazochrome sodium sulfonate and adrenochrome monoaminoguanidine methanesulfonate. Among antituberculotics are isoniazid, ethambutol and sodium p-aminosalicylate. The hormone drugs are exemplified by prednisolone succinate, prednisolone sodium phosphate, dexamethasone sodium sulfate, betamethasone sodium phosphate, hexestrol phosphate, hexestrol acetate and methimazole. The antinarcotic agents include, among others, levallorphan tartrate, nalorphine hydrochloride and naloxone hydrochloride.

Brief Summary Text (79):
Derivatives of Vitamin B.sub.12 for use as carriers for microparticles include the anilide, ethylamide, monocarboxylic and dicarboxylic acid derivatives of Vitamin B.sub.12 and its analogues as well as tricarboxylic acid or proprionamide derivatives of Vitamin B.sub.12 or its analogues. They would also include molecules in which alterations or substitutions had been performed to the Corrin ring [viz:-cyano (13-epi) cobalamin Co a-(a 5,6-dimethylbenzimidazoyl)-Co, b-cyano-(13-epi) cobamic a,b,c,d,g, pentaamide, adenosyl-10-chlorocobalamin, dicyanobyrinic heptamethyl ester, cyanoaquacobyrinic acid pentaamide], or where cobalt had been replaced by another metal ion (viz:- nickel, zinc, etc) or various anion or alkyl substituents to the corrin ring such that the binding capacity of the molecule to intrinsic factor is unaffected. The mucosal epithelial cells will take up the intrinsic factor-vitamin B.sub.12 complex including the microparticle, such as a microsphere or microcapsule attached to the vitamin B.sub.12 (or suitable analogue) and transepithelially transport the microsphere or microcapsule and deliver them into the circulation where the enclosed substance such as a hormone, drug, immunogen, or DNA or RNA (such as ribozyme) component, molecule or analogues thereof can act.

Brief Summary Text (81):
Similarly, if a microparticle, such as a microsphere or microcapsule is administered orally and complexed to a carrier protein possessing binding activity to the mucosal epithelium, the cells of the mucosal epithelium take up those molecules including the microparticles, such as microspheres or microcapsules attached to the carrier proteins and present the microsphere or microcapsule to the circulation where the substance such as a drug, hormone, immunogen or DNA or RNA (such as ribozyme)

component, molecule or analogues thereof enclosed therein can act.

Brief Summary Text (105):
Advantageously, using a complex of the present invention, a substance such as a hormone, drug or immunogen can be presented via the mucosal epithelium of a host, in a pharmaceutically active form to the circulation or lymphatic drainage system of a host. Initially, microparticles such as microspheres or microcapsules, containing a substance such as a pharmaceutically active agent, are prepared and linked, generally covalently, to a suitable carrier (generally a mucosal binding protein or Vitamin B.sub.12 or an analogue or derivative thereof) such that the carrier maintains its ability to interact with the intestinal mucosa or intrinsic factor (respectively). Then the microparticles are administered orally to a host and as a result of this administration the carrier-microparticles and the substance contained therein pass into the circulation or lymphatic drainage system of the host. In this fashion the substance is protected from the degradative contents of the intestinal milieu, and the uptake capacity of the carrier is amplified.

Brief Summary Text (107):
The present invention relies on the ability to entrap substances, which are generally small molecules, such as hormones, proteins, peptides, drugs, etc, within a matrix or capsule, generally fabricated from a suitable polymer, in such a way as to form very small microparticles such as microcapsules or microspheres. Once trapped within these microparticles it is possible using suitable chemistry to link, generally covalently link, these microparticles to a suitable carrier.

Brief Summary Text (113):
Microspheres containing a substance such as a hormone, drug, immunogen, or DNA or RNA (such as ribozyme) component, molecule or analogues thereof, are prepared typically by one or more of a number of techniques commonly known to those knowledgeable in the art, including: Solvent evaporation, Complex coacervation, Polymer/polymer incompatibility, Gelation, Interfacial polymerization and Thermal denaturation.

Brief Summary Paragraph Table (1):
TABLE 1 ____ Amplification of the Vitamin B.sub.12 uptake capacity by the incorporation of pharmaceutically active agents into microspheres. Total delivery to man. Microsphere Weight of Weight of diameter Volume micro- pharma- Quantity (nm) (cc) spheres.sup.1 ceutical.sup.2 delivered.sup.3 ____ -- -- -- 1 nm 0.001-0.01 nm -- -- -- 1 nm + VB.sub.12 0.1-1 nm 20 4 .times. 10.sup.-18 2.4 mg 240 .mu.g 0.24-2.4 .mu.g 20 4 .times. 10.sup.-18 2.4 mg 240 .mu.g + VB.sub.12 0.24-240 .mu.g 200 4 .times. 10.sup.-15 2.4 gm 240 mg 0.24-2.4 mg 200 4 .times. 10.sup.-15 2.4 gm 240 mg + VB.sub.12 0.24-240 mg 2000 4 .times. 10.sup.-12 2.4 kg 240 gm 0.24-2.4 gm 2000 4 .times. 10.sup.-12 2.4 kg 240 gm + VB.sub.12 0.24-240 gm ____ .sup.1 Data is calculated from the uptake capacity for Vitamin B.sub.12 o 1 nanomole per feed in man, which represents 6 .times. 10.sup.14 molecule of Vitamin B.sub.12. .sup.2 Each microsphere would be loaded to a 10% drug loading. .sup.3 With normal unassisted uptake approximately 0.1-1% of the dose of an orally administered pharmaceutical will cross the intestinal wall and enter the circulation. The Vitamin B.sub.12 uptake mechanism has the capacity to amplify this uptake by at least one hundred fold.

Detailed Description Text (72):
Oppenheim R. C. (1984) in "Polymeric Microparticles" (Guiot, P and Couvreur, P. Eds.) CRC Press, Boca Raton. Oppenheim R. C., Gipps, E. M. Forbes, J. F. and Whitehead R. H. (1984) in "Microspheres and Drug Therapy" (Davis, S. S., Illum, L., McVie, J. G. and Tomlinson, E. Eds) Elsevier Science Publishers B. V. Oppenheim, R. C., Stewart, N. F., Gordon, L. and Patel, H. M. (1982) Drug Devel. Indust. Pharm. 8: 531-546. Allen, R. H. and Majerus, P. W. (1972) J.Biol. Chem. 247: 7702-7717.

CLAIMS:

5. A complex according to claim 1, wherein the microsphere or microcapsule entraps or encapsulates a hormone, drug, immunogen, ribozyme, DNA or RNA.

6. A complex according to claim 2, wherein the microsphere or microcapsule is capable of entrapping or encapsulating a compound selected from the group consisting of a hormone, drug, immunogen, DNA or RNA.